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REMARKS

Status of Claims

This submission is in response to the Official Action dated June 6, 2003. Claims 1, 10, 14, and 20 have been amended. Specifically, claim 1 has been amended to indicate that "the immunogenic substance is not DNA derived from cytomegalovirus." Support for this amendment can be found on page 14, line 33 to page 15, line 18. Claims 10 and 20 have been amended to clarify the listing of adjuvants and to indicate the proviso that magnesium hydroxide is not in combination with aluminum hydroxide or aluminum oxide. Support for these amendments can be found in the specification on page 11, line 13, in original claim 1 and on page 28, lines 7-9. Claim 14 has been amended to clarify the amount of adjuvant being claimed. Support for this amendment can be found on page 20, line 34 to page 21, line 2. New claims 65 and 66 have been added. Support for new claim 65 is found in original claim and on page 21, lines 1-2. Support for new claim 66 can be found in original claim 1, an d in the specification on page 15, lines 1-6. Claims 3, 21-47, 51-57, and 60-64 have been withdrawn. Claims 48-50 were previously cancelled. Therefore, claims 1, 2, 4-20, 58 and 59 are the pending claims. No new matter is added by any of the above-noted amendments. Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Objections

The Examiner has objected to the preliminary amendment filed November 26, 2001 under 35 U.S.C. §132 as introducing new matter. Specifically, the Examiner states that the incorporation of the applications on page 1, line 1 constitutes new matter. In response, applicants respectfully submit that the claim to priority has been corrected.

It is therefore submitted that the specification as amended has overcome the objection and applicants respectfully request the Examiner to withdraw the objection.

The Examiner has also objected to the title of the invention as not descriptive

to the invention to which the claims are directed. In response, Applicants have amended the title as suggested in the Office Action. Therefore, Applicants submit that the objection is overcome.

The Examiner has also objected to the disclosure of "Rf" as a Group 4 element of the period table. In particular, the Examiner has indicated that this is not a recognized element within the standard Periodic Table. Applicants respectfully traverse this objection, and respectfully submit that "Rf" is a recognized Group 4 element of the Periodic Table. For example, the Examiner's attention is respectfully directed to the Periodic Table of Elements attached hereto at Exhibit Tab A. This Periodic Table, which is reproduced from a standard chemistry text book (Andrew Streitwieser & Clayton H. Heathcock, *Introduction to Organic Chemistry*, 3rd Edition (1985), Macmillan Publishing Company, New York). This Periodic Table clearly shows "Rf" as element number 104. Applicants also invite the Examiner's attention to page B-15 from the *CRC Handbook of Chemistry and Physics*, 66th Edition (1985), CRC Press, Inc., Boca Raton, Florida, which is attached hereto at Exhibit Tab B. This page discusses Element 104, and notes that the name proposed for this element is "rutherfordium (symbol Rf) in honor of Ernest R. Rutherford, New Zealand physicist." In view of this evidence, hence, "Rf" is an element well known and recognized in the art. Applicants therefore respectfully submit that the Examiner's objections to that term should be withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 1, 2, 4-20, 58, and 59 under 35 U.S.C. § 112, second paragraph as indefinite. Specifically, the Examiner states that claims 1, 2, 4-20, 58 and 59 include reference to "Rf" which, according to the Examiner, is not a recognized designation on the Periodic Table. This rejection is respectfully traversed, for the reasons set forth above. In particular, and as demonstrated at Exhibit Tabs A and B, "Rf" is a symbol known and recognized in the art as designating the element "rutherfordium" – *i.e.*, element 104 in the Periodic Table of Elements. Hence, this rejection for indefiniteness should be withdrawn.

The Examiner also rejects claims 10 and 20 as being confusing by contradicting the limitations of claim 1. In response, applicants have amended claims 10 and 20 to exclude "calcium phosphate" and have included the proviso "that the salt is not magnesium hydroxide in combination with aluminum hydroxide or aluminum oxide". Support for the amendments can be found in the specification on page 11, line 13, in original claim 1 and on page 28, lines 7-9. Applicants make this amendment for purposes of clarification and respectfully request the rejection be withdrawn.

The Examiner has also rejected claim 14 for the improper use of indicated amounts of adjuvant recited in the claims. Specifically, the Examiner rejects the language "such as ... 12M". In response, applicants have amended claim 14 to remove the language "such as from about 0.004 to about 12M". Applicants have added new claim 65 to reflect the omitted range. Applicants therefore respectfully request that the rejection be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 1, 2, 4-8, 11-13, 16, 58, and 59 as anticipated under 35 U.S.C. § 102(e) by U.S. Patent No. 6,448,389 (to Gonczol et al.). According to the Examiner, Gonczol teaches a vaccine formulation comprising DNA molecules expressing gB to induce immune response to HCMV (human cytomegalovirus) as well as suspending DNA formulations in carriers and incorporating magnesium hydroxide adjuvant. As stated by the Examiner, Gonczol also teaches administration by injection.

The rejection is respectfully traversed, and reconsideration is respectfully requested.

In response, applicants submit that Gonczol's teaching is restricted to DNA comprising at least one human cytomegalovirus antigen. See '389 Patent, col. 1, lines 59-65. In the present invention, Claim 1, as amended, includes a proviso of the immunogenic substance excluding DNA derived from cytomegalovirus. This amendment is supported in the specification on page 14, line, 33 to page 15, line 18,

where suitable immunogenic substances are exemplified, including cytomegalovirus. While applicants have disclosed this specific source, the subject matter is no longer claimed. Therefore, the presently claimed invention is a different formulation than that taught in Gonczol. In view of the foregoing support in the specification discussed above for the previous amendment to claim 1, applicants respectfully submit that no new matter is added, and that the rejection on these grounds should be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 9, 10 and 20 as unpatentable under 35 U.S.C. § 103 over Gonczol in view of Vogel et al. According to the Examiner, Gonczol "does not teach or suggest additionally adding a recited adjuvant in the claims", but the reference teaches more than one adjuvant. Furthermore, the Examiner states that Vogel provides the teaching of known adjuvants. According to the Examiner, one skilled in the art would have combined the references to arrive at the present invention.

The rejection is respectfully traversed, and reconsideration is respectfully requested. As presented above, applicants submit that Gonczol does not have the same formulation as the presently claimed invention in amended claim 1, and thus claims 9, 10 and 20 are patentable for the same reasons set forth above. Adding the teachings of known adjuvants of Vogel would not have made the presently claimed invention obvious. Therefore, applicants respectfully request that the rejections be withdrawn.

The Examiner has rejected claims 1, 2, 4-8, 11-13, 18, 58 and 59 as unpatentable under 35 U.S.C. § 103 over U.S. Patent No. 6,362,236 (to Aviram et al.) in view of U.S. Patent No. 5,464,633 (to Conte et al.). According to the Examiner, Aviram teaches compositions and methods of administering a hydrolated cholesterol lower agent for parenteral administration, but does not teach titanium dioxide as an adjuvant. The Examiner states that Conte provides the teaching that titanium dioxide has adjuvant properties well known in the art, and that it is well known in the art to use adjuvants in vaccine formulations. Therefore, one skilled in

the art would have combined the noted references to arrive at the presently claimed invention.

The rejection is respectfully traversed, and reconsideration is respectfully requested. In response, applicants submit that the combination of references would not achieve the presently claimed invention. Aviram discloses a formulation wherein the active compound is nor not an immunogen, but is instead a cholesterol-lowering agent. These compounds have molecular weights that are significantly lower than the molecular weights of immunogens according to the present invention.

Moreover, the Examiner has apparently conceded that titanium dioxide does not appear to function as an adjuvant, since Aviram teaches that titanium can function as an excipient or carrier, e.g., in compressed tablets or gelatine capsules (col. 14, lines 13-14). Applicants submit that, contrary to what is stated in the Office Action, Conte does not teach that titanium dioxide may be used as an adjuvant. Rather, at column 6, lines 17-18, Conte states (emphasis added):

> "In such case beside the basic polymeric material as before described plasticizing agents as ... and **opacity agents** as titanium dioxide **and other adjuvants** ... may be used"

Conte teaches that titanium dioxide is used as an opacity agent, i.e., titanium dioxide used as a coloring agent applying white pigment and protection against light-induced degradation of the active substance.

Furthermore, Conte is concerned with oral tablets for slow-release of active substances and is thus not related to the field of parenteral vaccines. The term "adjuvant" in context with oral slow-release tablets can thus not be understood to comprise parenteral vaccine formulations. It is not obvious to one skilled in the art to use titanium dioxide as an adjuvant in parenteral vaccine formulations, nor is there any teaching that titanium dioxide would have adjuvant properties. Therefore, applicants submit that one skilled in the art would have no motivation or guidance to expect that titanium dioxide can function as an adjuvant in immunogenic

formulations.

Therefore, it would not have been obvious to one skilled in the art to combine the teachings of Aviram and Conte to arrive at the presently claimed invention. Applicants respectfully request that the rejection be withdrawn.

The Examiner has also rejected claim 19 as unpatentable under 35 U.S.C. § 103 over Gonczol in view of Aviram et al. and Conte et al. as applied to the claims noted above. The rejection is respectfully traversed, and reconsideration is respectfully requested. As presented above, applicants submit that Gonczol does not have the same formulation as the presently claimed invention in amended claim 1, and thus claim 19 is patentable for the same reasons set forth above. Adding the teachings of Aviram and Conte would not have made the presently claimed invention obvious (also discussed above). Therefore, applicants respectfully request that the rejections be withdrawn.

Allowance of Claims

Applicants gratefully acknowledge the allowance of claim 17.

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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THIRD EDITION

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UNIVERSITY OF CALIFORNIA, BERKELEY

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Periodic Table of the Elements

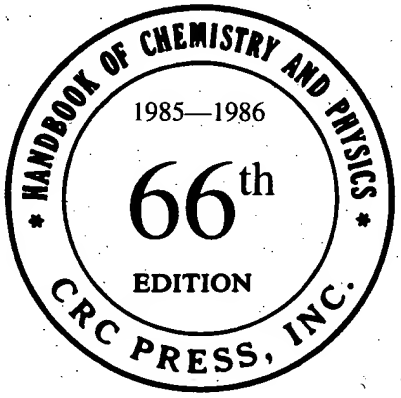
																	2 **He** 4.003
3 **Li** 6.94	4 **Be** 9.01											5 **B** 10.81	6 **C** 12.011	7 **N** 14.01	8 **O** 16.00	9 **F** 19.00	10 **Ne** 20.18
11 **Na** 22.99	12 **Mg** 24.31											13 **Al** 26.98	14 **Si** 28.09	15 **P** 30.97	16 **S** 32.06	17 **Cl** 35.45	18 **Ar** 39.95
19 **K** 39.10	20 **Ca** 40.08	21 **Sc** 44.96	22 **Ti** 47.90	23 **V** 50.94	24 **Cr** 52.00	25 **Mn** 54.94	26 **Fe** 55.85	27 **Co** 58.93	28 **Ni** 58.71	29 **Cu** 63.55	30 **Zn** 65.37	31 **Ga** 69.72	32 **Ge** 72.59	33 **As** 74.92	34 **Se** 78.96	35 **Br** 79.90	36 **Kr** 83.80
37 **Rb** 85.47	38 **Sr** 87.62	39 **Y** 88.91	40 **Zr** 91.22	41 **Nb** 92.91	42 **Mo** 95.94	43 **Tc** 98.91	44 **Ru** 101.07	45 **Rh** 102.91	46 **Pd** 106.4	47 **Ag** 107.87	48 **Cd** 112.40	49 **In** 114.82	50 **Sn** 118.69	51 **Sb** 121.75	52 **Te** 127.60	53 **I** 126.90	54 **Xe** 131.30
55 **Cs** 132.91	56 **Ba** 137.34	57 **La** 138.91	72 **Hf** 178.49	73 **Ta** 180.95	74 **W** 183.85	75 **Re** 186.2	76 **Os** 190.2	77 **Ir** 192.2	78 **Pt** 195.09	79 **Au** 196.97	80 **Hg** 200.59	81 **Tl** 204.37	82 **Pb** 207.19	83 **Bi** 208.98	84 **Po** (209)	85 **At** (210)	86 **Rn** (222)
87 **Fr** (223)	88 **Ra** 226.03	89 **Ac** (227)	104 **(Rf)** (261)	105 **(Ha)** (262)	106 (263)												

Lanthanides	58 **Ce** 140.12	59 **Pr** 140.91	60 **Nd** 144.24	61 **Pm** (145)	62 **Sm** 150.35	63 **Eu** 151.96	64 **Gd** 157.25	65 **Tb** 158.93	66 **Dy** 162.50	67 **Ho** 164.93	68 **Er** 167.26	69 **Tm** 168.93	70 **Yb** 173.04	71 **Lu** 174.97
Actinides	90 **Th** 232.04	91 **Pa** (231)	92 **U** 238.03	93 **Np** (237)	94 **Pu** (244)	95 **Am** (243)	96 **Cm** (247)	97 **Bk** (249)	98 **Cf** (249)	99 **Es** (254)	100 **Fm** (257)	101 **Md** (258)	102 **No** (259)	103 **Lr** (260)

Numbers in parentheses: available radioactive isotope of longest half-life.

CRC Handbook of Chemistry and Physics

A Ready-Reference Book of Chemical and Physical Data



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readily without swelling or contracting under prolonged neutron bombardment. In combination with vanadium and other earth, dysprosium has been used in making laser materials. Dysprosium-cadmium calcogenides, as sources of infrared radiation, have been used for studying chemical reactions. The cost of dysprosium metal has dropped in recent years since the development of ion- exchange and solvent extraction techniques, and the discovery of large ore bodies. The metal is still expensive, however, and costs about $3/g in purities of 99+ %.

Einsteinium — (Albert Einstein), Es; at wt. (252); at no. 99. Einstenium, the seventh transuranic element of the actinide series to be discovered, was identified by Ghiorso and co-workers at Berkeley in December 1952 in debris from the first large thermonuclear or "hydrogen" bomb explosion, which took place in the Pacific in November 1952. The isotope produced was the 20-day Es^{253} isotope. In 1961, a sufficient amount of einsteinium was produced to permit separation of a macroscopic amount of Es^{253}. This sample weighed about 0.01 μg. A special magnetic-type balance was used in making this determination. Es^{253} so produced was used to produce mendelevium (Element 101). About 3 μg of einsteinium has been produced at Oak Ridge National Laboratores by irradiating for several years kilogram quantities of Pu^{239} in a reactor to produce Pu^{242}. This was then fabricated into pellets of plutonium oxide and aluminum powder, and loaded into target rods for an initial 1-year irradiation at the A.E.C.'s Savannah River Plant, followed by irradiation in a HFIR (High Flux Isotopic Reactor). After 4 months in the HFIR the targets were removed for chemical separation of the einsteinium from californium. Eleven isotopes of einsteinium are now recognized. Es^{254} has the longest half-life (276 days). Tracer studies using Es^{253} show that einsteinium has chemical properties typical of a heavy trivalent, actinide element.

Element 104 — In 1964, workers of the Joint Nuclear Research Institute at Dubna (U.S.S.R.) bombarded plutonium with accelerated 113 to 115 MeV neon ions. By measuring fission tracks in a special glass with a microscope, they detected an isotope that decays by spontaneous fission. They suggested that this isotope, which had a half-life of 0.3 ± 0.1 sec might be 104^{260}, produced by the following reaction:

$$_{94}Pu^{242} + {}_{10}Ne^{22} \longrightarrow 104^{260} + 4n$$

Element 104, the first *transactinide* element, is expected to have chemical properties similar to those of hafnium. It would, for example, form a relatively volatile compound with chlorine (a tetrachloride). The Soviet scientists have performed experiments aimed at chemical identification, and have attempted to show that the 0.3-sec activity is more volatile than that of the relatively nonvolatile actinide trichlorides. This experiment does not fulfill the test of chemically separating the new element from all others, but it provides important evidence for evaluation. New data, reportedly issued by Soviet scientists, have reduced the half-life of the isotope they worked with from 0.3 to 0.15 sec. The Dubna scientists suggest the name *kurchatovium* and symbol *Ku* for Element 104, in honor of Igor Vasilevich Kurchatov (1903-1960), late Head of Soviet Nuclear Research. In 1969, Ghiorso, Nurmia, Harris, K.A.Y. Eskola, and P.L. Eskola of the University of California at Berkeley reported they had positively identified two, and possibly three, isotopes of Element 104. The group also indicated that after repeated attempts so far they have been unable to produce isotope 104^{260} reported by the Dubna group in 1964. The discoveries at Berkeley were made by bombarding a target of Cf^{249} with C^{12} nuclei of 71 MeV, and C^{13} nuclei of 69 MeV. The combination of C^{12} with Cf^{249} followed by instant emission of four neutrons produced Element 104^{257}. This isotope has a half-life of 4 to 5 sec, decaying by emitting an alpha particle into No^{253}, with a half-life of 105 sec. The same reaction, except with the emission of three neutrons, was thought to have produced 104^{258}, with a half-life of about 1/100 sec. Element 104^{259} is formed by the merging of a C^{13} nuclei with Cf^{249}, followed by emission of three neutrons. This isotope has a half-life of 3 to 4 sec, and decays by emitting an alpha particle into No 255, which has a half-life of 185 sec. Thousands of atoms of 104^{257} and 104^{259} have been detected. The Berkeley group believe their identification of 104^{258} is correct, but they do not attach the same degree of confidence to this work as to their work on 104^{257} and 104^{259}. The Berkeley group proposes for the new element the name *rutherfordium* (symbol Rf), in honor of Ernest R. Rutherford, New Zealand physicist. The claims for discovery and the naming of Element 104 are still in question.

Element 105 — In 1967 G.N. Flerov reported that a Soviet team working at the Joint Institute for Nuclear Research at Dubna may have produced a few atoms of 105^{260} and 105^{261} by bombarding Am^{243} with Ne^{22}. Their evidence was based on time-coincidence measurements of alpha energies. More recently, it was reported that early in 1970 Dubna scientists synthesized Element 105 and that by the end of April 1970 "had investigated all the types of decay of the new element and had determined its chemical properties." The Soviet group has not proposed a name for Element 105. In late April 1970, it was announced that Ghiorso, Nurmia, Harris, K.A.Y. Eskola, and P.L.Eskola, working at the University of California at Berkeley, had positively identified Element 105. The discovery was made by bombarding a target of Cf^{249} with a beam of 84 MeV nitrogen nuclei in the Heavy Ion Linear Accelerator (HILAC). When a N^{15} nuclei is absorbed by a Cf^{249} nucleus, four neutrons are emitted and a new atom of 105^{260} with a half-life of 1.6 sec is formed. While the first atoms of Element 105 are said to have been detected conclusively on March 5, 1970, there is evidence that Element 105 had been formed in Berkeley experiments a year earlier by the method described. Ghiorso and his associates have attempted to confirm Soviet findings by more sophisticated methods without success. The Berkeley Group proposes the name *hahnium*, after the late German scientist Otto Hahn (1879-1968), and *Ha* for the chemical symbol.

More recently, in October 1971, it was announced that two new isotopes of Element 105 were synthesized with the heavy ion linear accelerator by A. Ghiorso and co-workers at Berkeley. Element 105^{261} was produced both by bombarding Cl^{250} with N^{15} and by bombarding Bk^{249} with O^{16}. The isotope emits 8.93-MeV α particles and decays to Lr^{257} with a half-life of about 1.8 sec. Element 105^{262} was produced by bombarding Bk^{249} with O^{18}. It emits 8.45 MeV α particles and decays to Lr^{258} with a half-life of about 40 sec.

Element 106 — In June 1974, members of the Joint Institute for Nuclear Research in Dubna, U.S.S.R., reported their discovery of Element 106, which they claim to have synthesized. In September 1974, workers of the Lawrence Berkeley and